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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

NEUER ET AL.

APPLICATION NO: 09/738,212

FILED: DECEMBER 15, 2000

Art Unit: 1617

Examiner: A. Berman

FOR: PHARMACEUTICAL COMPOSITIONS OF MACROLIDES OR CYCLOSPORINE WITH A POLYETHOXYLATED SATURATED HYDROXY-FATTY ACID

Assistant Commissioner for Patents
Washington, D.C. 20231

BRIEF ON APPEAL

Sir:

This appeal is lodged in response to a Final Rejection dated May 21, 2002, finally rejecting claims 21-30 and 33. Applicants request reconsideration of the rejections and reversal of the Final Rejection.

1. Real Party In Interest:

The real party in interest is Novartis AG.

2. Related Appeals and Interferences:

None.

3. Status of Claims:

Claims 21-33 (Appendix I) are pending. Claims 21-30 and 33 are under Final Rejection and are now on appeal. Claims 31 and 32 are withdrawn from consideration.

4. Status of the Amendments:

All the original claims have been canceled. Claims 21-33 were added by amendment dated January 16, 2002.

5. Summary of the Invention:

The invention is directed to a hard gelatin capsule comprising cyclosporin as active ingredient, a polyethoxylated saturated hydroxy-fatty acid, and a C_2-C_3 alcohol.

The invention is also directed to a capsule as above further comprising triesters of fatty acids and optional ingredients.

6. Issues:

1. Whether claim 33 is indefinite.

2. Whether the claimed compositions are obvious in view of the art.

3. Whether double-patenting rejections over applications 09/690,400, 09/605,512, and 09/547,802 are proper.

7. Grouping of the Appealed Claims:

The claims on appeal may be grouped as: 1) claims 21-30; and 2) claim 33.

8. Arguments:

1. Is claim 33 indefinite?

The Examiner argues that it is unclear whether this claim is directed to 1) A + B or C; 2) A +B; or 3) A + C. A clear reading of the claim shows that it is directed to A + B or C. The reasons for the Examiner's additional readings of the claim are not apparent. The Examiner further rejects the claim because it is not clear what the basis of the "smaller proportions" is. Again, it is deemed that the meaning is clear: The unsaturated fatty acid glycerides are present in a lesser amount than the ricinoleic acid glycerides.

2. Rejection under 35 USC 103

Claims 21-30 and 33 are rejected under 35 USC 103 as obvious over the combination of Hauer (US '625) and Orban (US '396). The rejection is traversed.

Because of their hydrophobic character, cyclosporins present highly specific difficulties in relation to administration and the formulation of oral compositions. In particular, it is difficult to produce pharmaceutical compositions showing stability, high biovailability and low intra- and inter-subject variability. As a general rule, when administered intravenously, active agents appear directly in the bloodstream, and are able to immediately produce their pharmacological effect. When administered orally, however, compositions have to enable effective resorption of the active agent from the stomach or gut lumen and achievement of consistent and appropriately high blood/blood-serum levels. It follows, that the effect of orally administering a composition suitable for intravenous application is unpredictable.

When one applies the above general rule to the present case, it can be seen that Orban discloses a cyclosporin containing composition for intravenous administration, whereas the present claims are directed solely to oral compositions. Specifically, the invention as presently claimed relates to compositions in the form of hard gelatin capsules. Col .4, example 1 of Orban discloses a composition containing cyclosporin, Solutol HS 15, and ethanol. The solution is homogenized, filtered, and has to be diluted prior to application by injection with an isotonic solution. The disadvantage of this preparation is that it has to be administered by trained personnel which includes inconvenience and discomfort for the patients. Moreover, sterility problems may arise. Nowhere in this reference is any teaching that this composition may also be used for oral administration. There is no teaching or suggestion that this composition may also be advantageous with respect to stability and bioavailability in medicaments for oral administration.

On the other hand, Hauer discloses a cyclosporin-containing composition in the form of a microemulsion-preconcentrate comprising a hydrophilic component, a lipophilic component, and a surfactant, e.g. a polyoxyethylene stearic acid ester. The present invention provides hard gelatin capsules comprising a polyethyoxylated saturated hydroxy-fatty acid.

There is no motivation to use the composition of Orban for oral administration. Thus, there would not have been any motivation to combine these references or to provide the hard gelatin capsules or of the present invention which may be administered orally, have satisfactory bioavailability, low intra- inter subject variability and stability. Hence, the present claims are not obvious over the art.

Further, claim 33 relates to a hard gelatin capsule additionally comprising a mono-, di-, and/or tri-glyceride of a C_{16}-C_{18} fatty acid and optional other ingredients. Orban discloses none of these compounds.

In construing the art, the Examiner must consider the teachings as a whole. When doing so, it is deemed that one of ordinary skill in the art would not combine these two references. It is deemed that, the Examiner has used hindsight selection in view of Applicants' specification to pick and choose these references and to select from them those portions which would support the rejection, which is not permitted.

3. Rejections for double-patenting.

These are provisional rejections. The propriety of these rejections can only be decided after the basis issue of patentability is resolved and the otherwise patentable claims herein compared with the claims patented or allowed in the other applications.

It is believed that claim 33 is not unclear and that the combination of references is improper but that even if proper would not make obvious to one skilled in the art the compositions of the invention.

It is also believed that the rejections for double patenting can only be resolved after otherwise allowable subject matter is identified.

Accordingly, reconsideration of the propriety of the outstanding rejections under 35 U.S.C. 112 and103 and allowance of the claims to issue as U.S. Letters Patent is respectfully solicited.

The Commissioner is hereby authorized to charge the fee under 37 CFR 1.17(c) of $320.00 to Deposit Account No. 19-0134

Respectfully submitted,

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Encls.: Appeal Brief in triplicate with Appendix
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APPENDIX I

21. (new) A hard gelatin capsule comprising
(a) a cyclosporin as active ingredient,
(b) a polyethoxylated saturated hydroxy-fatty acid, and
(c) a C_2-C_3 alcohol having one or two hydroxy groups.

22. (new) A hard gelatin capsule of claim 21 wherein the polyethoxylated saturated hydroxy-fatty acid is the sole surfactant.

23. (new) A hard gelatin capsule of claim 21 wherein the cyclosporin is Cyclosporin A.

24. (new) A hard gelatin capsule of claim 21 wherein the polyethoxylated saturated hydroxy-fatty acid comprises poylethylene glycol-660-12-hydroxy-stearate.

25. (new) A hard gelatin capsule of claim 21 wherein the C_2-C_3 alcohol comprises ethanol, proypylene glycol, or ethanol and proypylene glycol.

26. (new) A hard gelatin capsule of claim 25 wherein the C_2-C_3 alcohol comprises ethanol.

27. (new) A hard gelatin capsule of claim 21 wherein the cyclosporin is present in an amount of between 1 to 20 wt-% based on the weight of the composition.

28. (new) A hard gelatin capsule of claim 21 wherein the polyethoxylated saturated hydroxy-fatty acid is present in an amount of between 15 to 95 wt-% based on the weight of the composition.

29. (new) A hard gelatin capsule of claim 21 wherein the C_2-C_3 alcohol is present in an amount of up to 40 wt-% based on the weight of the composition.

30. (new) A hard gelatin capsule of claim 21 wherein components (a), (b), and (c) are present in the ratio 1 to 4 parts (a) : 6 to 15 parts (b) : 3 to 12 parts (c), all parts by weight.

31. (new) A method of treating or preventing organ or tissue transplant rejection which comprises administering to a patient in need thereof a hard gelatin capsule of claim 21.

32. (new) A method which comprises orally administering a capsule of claim 21 to a patient in need thereof.

33. (new) A hard gelatin capsule of claim 21 further comprising

(d) mono-, di- and/or triesters of fatty acids, and optionally

(e) ricinoleic acid glyceride(s) together with smaller proportions of multiply unsaturated fatty acid glycerides or castor oil

as a unit dosage form.